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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,418	04/26/2006	Shirou Sawa	2006_0177A	7556

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EXAMINER	
HUANG, GIGI GEORGIANA	
ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
05/13/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/568,418	SAWA ET AL.	
	Examiner	Art Unit	
	GIGI HUANG	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-7 and 9-11* is/are pending in the application.

4a) Of the above claim(s) *5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,7 and 9-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The response filed February 5, 2010 has been received, entered and carefully considered. The response affects the instant application accordingly:

a. Claims 1, 5-7, 9-11 have been amended.

2. Claims 1, 3, 5-7, 9-11 are pending in the case.

3. Claims 1, 3, 6-7, 9-11 are present for examination.

4. The text of those sections of title 35.U.S. Code not included in this action can be found in the prior Office action.

5. All grounds not addressed in the action are withdrawn or moot.

6. New grounds of rejection are set forth in the current office action.

Election/Restrictions

7. As the indefiniteness for claim 5 is now rectified, the subject matter for claim 5 is to a non-elected species and non-elected grouping (amino acids) of organic amines, and is withdrawn from examination as being to the non-elected subject matter.

New Grounds of Rejection

Due to the amendment of the claims the new grounds of rejection are applied:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claim 1, 3, 6-7, 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ogawa et al (U.S. Pat. No. 4910225) in view of Kessler (U.S. Pat.5849291).

Ogawa teaches a method of treating inflammatory eye disease such as uveitis and conjunctivitis, with an ophthalmic composition comprised of a benzoylphenylacetic acid or its salt or the hydrate, with buffers, and optionally with additional pharmaceutical actives (e.g. anti-nflammatories) and excipients (e.g. an isotonizing agent, a preservative, a chelating agent).

The concentration of the benzoylphenylacetic acid compound can range from about 0.001% to about 10%, preferably in the range of 0.01 to about 5%. The composition can be in the form of a solution (aqueous and non-aqueous) and be administered as eye drops, ointments and any other known compositions for topical administration to the eye. The eye drops are to be administered one to several drops per dose in a frequency of once to four times a day according to the clinical condition. The dosage may be adjusted according to symptoms.

The examples teach compositions comprising the specific drug sodium 3-(4-bromobenzoyl) 2-aminophenylacetate/monohydrate at 0.1% (claimed instant compound) with excipients including buffers such as boric acid-borax (sodium borate) and sodium monohydrogen phosphate-sodium dihydrogen phosphate at about 1.0%w/v(Experimental Example 3-4),about 1.5%w/v (Experimental Example 5-6), and in ophthalmic solutions at certain points ranging from about 0.2%w/v to 2.25%w/v (about 0.2%w/v-Example 9, about 0.7%w/v-Example 7, about 1.5%w/v-Example 8, 2.25%w/v-Example 6). The recitation of the maintenance of bromfenac in the vitreous humor is a

recitation of intended effect which is intrinsically met when the components present in the composition (e.g. bromfenac, the organic amine) and the mode of administration are met as the results are the same as any component or step that materially affects the composition and its properties would have to be present in the claim to be commensurate in scope (Abstract, Col. 1, lines 33-38, 60-68, Col. 2, lines 1-36, 45-68, Col. 3, lines 30-54, Col. 4, lines 20-68, Col.5, lines 1-15-23, Col.6, lines 20-48, 53-68, Col.7, lines 1-68, Col8, lines 1-20, 25-68, Col.9, Example 1-2, Col.10, Example 6-7).

Ogawa et al. does not expressly teach the incorporation of the specifically claimed aminoalkylsulfonic acids, alkanolamine, or the piperazine.

Kessler teaches known buffers for ophthalmic compositions such as Na2HPO4-NaH2PO4 (sodium monohydrogen phosphate-sodium dihydrogen phosphate), boric acid-sodium borate, and Good Buffers such as Tris (also known as trometamol), MES, PIPES (1,4-bis(2-sulfoethyl)piperazine, and ACES which are aminoalkyl sulfonic acid compounds (see Penny); and that these buffers are functional equivalents (Col. 7 line 3-16).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute a Good buffer such as Tris or PIPES, as suggested by Kessler, and produce the instant invention. It would have been obvious to one of skill in the art to substitute one known buffer (boric acid-borax, sodium monohydrogen phosphate-sodium dihydrogen phosphate) for another known buffer such as Tris or PIPES as they are functional equivalents when motivated by pricing, availability, or desired properties of the pH range of the final product. When the buffer

Tris/PIPES are substitituted in the exemplified compositions of Ogawa, the component is at about 0.2%w/v-Example 9, 0.7%w/v- Example 7, and about 1.5%- Example 8, meeting the claims.

One of ordinary skill in the art would have been motivated to do this as it is desirable for manufacturers to have analogous choices to substitute the buffer when motivated by pricing, availability, or desired pH range and stability for the final product.

9. Claims 1, 3, 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ogawa et al (U.S. Pat. No. 4910225) in view of Kato (U.S. Pat. 5945121).

Ogawa teaches a method of treating inflammatory eye disease such as uveitis and conjunctivitis, with an ophthalmic composition comprised of a benzoylphenylacetic acid or its salt or the hydrate, with buffers, and optionally with additional pharmaceutical actives (e.g. anti-nflammatories) and excipients (e.g. an isotonizing agent, a preservative, a chelating agent).

The concentration of the benzoylphenylacetic acid compound can range from about 0.001% to about 10%, preferably in the range of 0.01 to about 5%. The composition can be in the form of a solution (aqueous and non-aqueous) and be administered as eye drops, ointments and any other known compositions for topical administration to the eye. The eye drops are to be administered one to several drops per dose in a frequency of once to four times a day according to the clinical condition. The dosage may be adjusted according to symptoms.

The examples teach compositions comprising the specific drug sodium 3-(4-bromobenzoyl) 2-aminophenylacetate/monohydrate at 0.1% (claimed instant

compound) with excipients including buffers such as boric acid-borax (sodium borate) and sodium monohydrogen phosphate-sodium dihydrogen phosphate at about 1.0%w/v(Experimental Example 3-4),about 1.5%w/v (Experimental Example 5-6), and in ophthalmic solutions at certain points ranging from about 0.2%w/v to 2.25%w/v (about 0.2%w/v-Example 9, about 0.7%w/v-Example 7, about 1.5%w/v-Example 8, 2.25%w/v-Example 6). The recitation of the maintenance of bromfenac in the vitreous humor is a recitation of intended effect which is intrinsically met when the components present in the composition (e.g. bromfenac, the organic amine) and the mode of administration are met as the results are the same as any component or step that materially affects the composition and its properties would have to be present in the claim to be commensurate in scope (Abstract, Col. 1, lines 33-38, 60-68, Col. 2, lines 1-36, 45-68, Col. 3, lines 30-54, Col. 4, lines 20-68, Col.5, lines 1-15-23, Col.6, lines 20-48, 53-68, Col.7, lines 1-68, Col8, lines 1-20, 25-68, Col.9, Example 1-2, Col.10, Example 6-7).

Ogawa et al. does not expressly teach the incorporation of taurine (aminoethylsulfonic acid) in the composition.

Kato et al. teaches that taurine is effective in the treatment of dry eye and other inflammatory conditions. Kato teaches that taurine when delivered to the eye is effective preferably in the range of 0.5 to 3.0% by weight for the treatment of dry eye (Col. 1, lines 10-48).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to incorporate taurine, as suggested by Kato et al., and produce the instant invention. It would have been obvious to one of skill in the art to

incorporate taurine to the composition for treating an inflammatory condition such as dry eye, as it is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; the idea of combining them flows logically from their having been individually taught in prior art.

One of ordinary skill in the art would have been motivated to do this as it is routine in the art to have combine of drugs for the same purpose to provide a more effective composition to treat the condition desired. Ogawa teaches explicitly, the incorporation of other active agents (Col. 4, lines 16-20) and Kato teaches that taurine is compatible with anti-inflammatories.

10. Claim 1, 3, 6-7, 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyagi et al. (U.S. Pat. 6281224) in view of Ogawa et al. (Effects of bromfenac sodium, nonsteroidal anti-inflammatory drug, on acute ocular inflammation).

Miyagi et al. teaches an ophthalmic solution with 0.01 to 0.5wt.% of pranoprofen and 0.1 to 5.0wt.% of an organic amine to treat an inflammatory disease of the eye. The conditions include those in the extraocular area and the anterior segment of the eye such as keratoconjunctivitis. Pranoprofen is a non-steroidal anti-inflammatory drug and the preferred organic amine include alkanolamines such as tromethamine, monoethanolamine, sulfoalkylpiperazine such as HEPES and PIPES, and sulfoalkyl alkylenediamines such as N,N'-bis(3-sulfopropyl)ethylenediamine which structurally can be viewed as within the class of aminoalkylsulfonic acids. There are examples exemplifying the composition with tromethamine and HEPES with pranoprofen at

various concentrations. Miyagi also teaches the administration of the composition to the eyes of 5-10 healthy male humans and having the degree of irritation evaluated (given once that day=once a day administration) where the composition with the organic amine (e.g. tromethamine or HEPES) had little ocular irritation.

Miyagi et al. does not expressly teach treatment of an inflammatory disease of the eye with a composition comprising bromfenac as the active agent .

Miyagi et al. does however teach the composition of a NSAID pranoprofen with the organic amine as addressed above.

Ogawa et al. (Effects of bromfenac...) teaches that bromfenac was more potent than pranoprofen in inhibiting ocular inflammation and may be useful in conjunctivitis and inflammation.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize bromfenac, as suggested by Ogawa et al. (Effects of bromfenac...), and produce the instant invention. It would have been obvious to one of skill in the art to substitute a more potent NSAIDS such as bromfenac for pranoprofen for the treatment of ocular inflammation such as conjunctivitis as bromfenac would be more effective that pranoprofen.

One of ordinary skill in the art would have been motivated to do this as it is desirable to utilize a more potent and effective drug for the composition to attain a greater therapeutic result and improved treatment.

Response to Arguments

11. In regards to Applicant's assertion for unexpected results for the instant claims with reference to Table 3, this has been fully considered but is not persuasive. The Table is not commensurate in scope with the claims and the showing is not unexpected and well within the variation present in the substitution of buffers. The Table presents the formulation results to have overlapping ranges

(e.g. Formula I boric acid: 214 ng/ml +/-46

Formula II trometamol: 260ng/ml +/- 45

Formula III taurine: 350+/-123 =

ranges of Formula I: 168-260

ranges of Formula II: 215-305

ranges of Formula III: 227-473;

plus formula I high point is 260, formula II low point is 215, formula III low point is 227);

wherein such overlap is evidence for a lack of unexpected results.

12. In regards to Applicant's arguments for Ogawa et al (U.S. Pat. No. 4910225) in view of Kessler (U.S. Pat.5849291), they have been fully considered but not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The arguments for unexpected results not persuasive and are addressed above. Ogawa teaches a method of treating inflammatory eye disease with an ophthalmic composition with examples utilizing the claimed compound within the claimed concentration with buffers such as boric acid-borax (sodium borate) and sodium monohydrogen phosphate-sodium dihydrogen phosphate. Kessler addresses that there are known functionally equivalent buffers in the ophthalmic art such as sodium monohydrogen phosphate-sodium dihydrogen phosphate, boric acid-sodium borate, and Good Buffers such as Tris (also known as trometamol) and PIPES (1,4-bis(2-sulfoethyl)piperazine, where it is obvious to substitute one ophthalmically known buffer for another. It is noted that only a section of Kessler is utilized merely to show that these functionally equivalent buffers are known in the ophthalmic art (Col. 7 line 3-16).

13. In regards to Applicant's arguments for Ogawa et al (U.S. Pat. No. 4910225) in view of Kato (U.S. Pat. 5945121), they have been fully considered but not persuasive. Applicant's argument is that Ogawa is directed to treating inflammatory disease of the eye and that Kato is directed to treating dry eye. This is not persuasive as dry eye (keratoconjunctivitis) is an inflammatory condition of the eye (see Baudouin and Lobefalo et al.) and Ogawa teaches the composition for treatment of inflammatory conditions of the eye including conjunctivitis (Abstract, Col. 1 line 33-37) and teaches the incorporation of additional pharmaceutical actives. Applicant's argument that the instant claim does not recited taurine as an active ingredient is not persuasive as taurine is intrinsically pharmaceutically active. The compound does not cease being pharmaceutically active if not cited to be an active in a claim. In response to applicant's

argument that taurine can maintain a therapeutically effective concentration of bromfenac is not persuasive, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). The assertion that the art would not have recognized the results of the combination were predictable is not persuasive as there is no evidence in the art to sustain the assertion or any teaching the art citing that these two elements should not be combined to assert unpredictability. As these two elements (taurine and bromfenac) are each already known in the art to be useful for the same purpose (treatment of inflammatory conditions- e.g. dry eye, conjunctivitis- for the eye), it is obvious to combine them for the very same treatment/purpose it is taught for with an expectation of predictability to be effective for treatment of the very same the condition particularly as Ogawa teaches for the inclusion of other actives. The arguments for unexpected results not persuasive and are addressed above.

14. Claim 1, 3, 5-7, 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyagi et al. (U.S. Pat. 6281224) in view of Ogawa et al. (Effects of bromfenac sodium, nonsteroidal anti-inflammatory drug, on acute ocular inflammation).

Claim 5 is withdrawn as being directed to non-elected subject matter due to amendment, the rejection is moot.

Applicant's arguments filed 2/5/2010 have been fully considered but they are not persuasive. Applicant asserts that the properties of pranoprofen are different from bromfenac, refers to Doutai, and that the compounds are structurally different. This is

not persuasive as pranoprofen and bromfenac are both non-steroidal anti-inflammatories (NSAIDS) and they are structurally similar enough to both function as NSAIDS and are ophthalmically acceptable for inflammation in the eye. As Ogawa expressly teaches that bromfenac is more potent that indomethacin and pranoprofen in ocular inflammation, it is obvious to substitute one NSAID for another, particularly if the NSAID (bromfenac) is more potent for the condition being treated (ocular inflammation). It is desirable to use a more effective/potent NSAID for the condition being treated. The reference to Doutai is not persuasive as it is not commensurate in scope with the claims and the showing of greater penetration of the bromfenac than pranoprofen actually goes to the rational to choose a better NSAID and perhaps why Ogawa found that bromfenac was more effective than pranoprofen. Additionally Miyagi et al. addresses that ophthalmic solutions that have no change in the composition can have excellent stability with little irritation to the eye can be accomplished by the addition of an organic amine such as Tris (tromethamine) or HEPES (Col. 1 line 59-63) wherein there is a reasonable expectation for the bromfenac to be stable in the solution with the organic amine, and when a solution is more stable, the content of the solution has a greater opportunity to be effective for the treatment of the condition.

Accordingly, the rejection is maintained.

Conclusion

15. Claims 1, 3, 6-7, 9-11 are rejected.

16. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GIGI HUANG whose telephone number is (571)272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fredrick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH
/Zohreh A Fay/
Primary Examiner, Art Unit 1612